Summary Minutes of the
Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC)
and the Drug Safety and Risk Management Advisory Committee (DSaRM)
March 10-11, 2010
Hilton Washington, DC/Silver Spring
The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland

All external requests for the meeting transcript should be submitted to the CDER, Freedom of Information office.

These summary minutes for the Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on April 19, 2010.

I certify that I attended the March 10-11, 2010 Joint Meeting of Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Kristine Khuc, Pharm.D.
Designated Federal Official,
PADAC

_____ /s/_____
Erik Swenson, M.D.
Acting Committee Chair,
PADAC

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)
Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC)
& Drug Safety and Risk Management Advisory Committee (DSaRM)
Hilton Washington, DC/Silver Spring
Silver Spring, Maryland
March 10-11, 2010
Summary Minutes

The following is an internal report which has not been reviewed. A verbatim transcript will be available in about 6 weeks, sent to the Division of Pulmonary, Allergy, and Rheumatology Products and posted on the FDA website at:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm199877.htm

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) met on March 10-11, 2010 at the Hilton Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Erik Swenson, M.D., (Acting Chair); the conflict of interest statement was read into the record by Kristine Khuc, Pharm.D. (Designated Federal Official). There were approximately 175 persons in attendance. There were 4 speakers for the Open Public Hearing session.

Attendance:
Pulmonary-Allergy Drugs Advisory Committee Members Present (Voting):
Paula Carvalho, M.D., Jerry Krishnan, M.D., Ph.D., Rodney Mullins (Consumer Representative), Thomas Alexander Platts-Mills, M.D., Ph.D., Carrie Redlich, M.D.

Pulmonary-Allergy Drugs Advisory Committee Members Present (Non-Voting):
Richard Hubbard, M.D. (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Present (Voting):
Judith Kramer, M.D., Elaine Morrato, Dr.P.H., Sidney Wolfe, M.D. (Consumer Representative)

Special Government Employee Consultants Present (Temporary Voting Members):
Erica Brittain, Ph.D., Avital Cnaan, Ph.D., Carl D'Angio, M.D., Robert Fink, M.D., Thomas Fleming, Ph.D., William Greene, Pharm.D., Jesse Joad, M.D., Charles Mouton, M.D., Dennis Ownby, M.D., Susan Roberts, Ph.D., Geoffrey Rosenthal, M.D., David Schoenfeld, Ph.D., Erik Swenson, M.D., Angelica Walden (Patient Representative)

FDA Participants Present (Non-Voting):
Badrul Chowdhury, M.D., Ph.D., Gerald Dal Pan, M.D., John Jenkins, M.D., Ann McMahon, M.D., Curtis Rosebraugh, M.D.

Open Public Hearing Presenters:
Bobby Lanier M.D., American College of Allergy, Asthma, and Immunology, Robert Lemanske, Jr., M.D**.,** American Academy of Allergy Asthma & Immunology, Nancy Sander, Allergy & Asthma Network Mothers of Asthmatics, W. Gerald Teague M.D., American Thoracic Society

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Designated Federal Official:
Kristine Khuc, Pharm.D.

Issue: The Committees discussed the design of medical research studies (known as "clinical trial design") to evaluate serious asthma outcomes (such as hospitalizations, a procedure using a breathing tube known as intubation, or death) with the use of the class of asthma medications known as long acting beta-2 adrenergic agonists in the treatment of asthma in adults, adolescents, and children.

The agenda was as follows:
-DAY ONE- March 10, 2010

8:00 a.m.	Call to Order Introduction of Committee	Erik Swenson, M.D. Acting Chair, PADAC
	Conflict of Interest Statement	Kristine Khuc, Pharm.D. Designated Federal Official, PADAC
	Opening Remarks	Curtis Rosebraugh, M.D. Director, Office of Drug Evaluation II Center for Drug Evaluation and Research (CDER) FDA
	FDA Presentation Background and Trial Design Considerations	Badrul Chowdhury, M.D., Ph.D Director, Division of Pulmonary and Allergy Products CDER, FDA
		Ann McMahon, M.D. Deputy Director, Division of Pharmacovigilance I Office of Surveillance and Epidemiology, CDER, FDA
		Andrew Mosholder, M.D. Medical Officer, Division of Epidemiology, Office of Surveillance and Epidemiology, CDER, FDA

Statistical Considerations	Benjamin Neustifter, Ph.D. Mathematical Statistician Office of Biostatistics Division VII CDER, FDA
Break	
FDA Presentation, cont.	
Drug Use Data	Grace Chai, Pharm.D. Drug Utilization Analyst Division of Epidemiology Office of Surveillance and Epidemiology, CDER, FDA
Summary/Questions	Badrul Chowdhury, M.D., Ph.D. Director, Division of Pulmonary and Allergy Products, CDER, FDA
Questions to FDA for Clarification	
Sponsor Presentation Evaluating Serious Outcomes in Asthma When LABA is Added to Inhaled Corticosteroid (ICS): Study Design Approaches	GlaxoSmithKline Katherine Knobil, M.D. GlaxoSmithKline Vice President, Respiratory Medicines Development Centre
Study Design Considerations For Rare Asthma-related Events	
Role of Observational Study Methods: Proposed Study	Carlos Camargo, M.D., Dr.P.H. Massachusetts General Hospital Harvard Medical School
Conclusions and Recommendations	Katherine Knobil, M.D. GlaxoSmithKline Vice President, Respiratory Medicines Development Centre
Lunch	
Questions to Sponsor for Clarification	

	Sponsor Presentation Design and Feasibility Assessments for a Postmarketing Safety Study for Symbicort	AstraZeneca Catherine Bonuccelli, M.D. Therapeutic Area Clinical Vice President, Respiratory & Inflammation AstraZeneca Kevin Carroll, M.Sc. VP Statistics & Chief Statistician AstraZeneca Tomas Andersson, M.D., Ph.D. Medical Science Director, Symbicort AstraZeneca
	Questions to Sponsor for Clarification	
	Break	
	Sponsor Presentation Regulatory History	Novartis Peter Fernandes, M.Pharm. Vice President, Drug Regulatory Affairs, Respiratory Novartis
	Foradil Safety in Asthma: Study Proposal	Steve Pascoe, MBBS, M.Sc. Clinical Science Unit Head, Respiratory Novartis
	Questions to Sponsor for Clarification	
5:10 p.m.	Adjourn	

<u>-DAY TWO- March 11, 2010</u>

8:10 a.m.	Call to Order Introduction of Committee	Erik Swenson, M.D. Acting Chair, PADAC

	Conflict of Interest Statement	Kristine Khuc, Pharm.D. Designated Federal Official, PADAC
	Welcome Remarks	Curtis Rosebraugh, M.D. Director, Office of Drug Evaluation II CDER, FDA
	Open Public Hearing	
	Questions for Clarification	
	Break	
	Committee Deliberations	
	Lunch	
	Continue Committee Deliberations	
2:55 p.m.	Adjourn	

Questions to the Committees:

Study Endpoints

1. A composite safety endpoint of asthma-related hospitalizations, asthma-related intubations, and asthma-related deaths is proposed for the adult/adolescent safety study.
Discuss:

a) The adequacy of the primary endpoint to address the safety concerns of LABAs for the treatment of asthma in adults/adolescents
b) What level of risk for LABAs would be considered acceptable to rule out; i.e., would be an acceptable upper bound of the 95% confidence interval?
c) Alternative endpoints that could be considered to evaluate the safety of LABAs for the treatment of asthma in adults/adolescents.

Committee members commented and expressed the following:

- *Concerns over conducting randomized clinical trial because of extreme difficulty in patient recruitment and limitations on a selective patient population.*

- *Feasibility of conducting a large practical randomized clinical trial with an enriched population consistent with current asthma treatment guidelines and to address quality of life endpoints (days of work missed, school absenteeism, nocturnal awakenings).*
- *Recommendation for the three sponsors to collaborate on a large international practical trial with central monitoring and adjudication of data.*
- *Stressed the labeling concept of LABA discontinuance should be dropped because it is not consistent with current guidelines and would inhibit design and recruitment to any planned prospective 6-12 month ICS + LABA vs. ICS trial in conjunction with the FDA.*
- *Pooling results across the drug products to get effects on hospitalizations and catastrophic endpoints by using approximately 50,000 patients and 80% power to rule out a 4 fold increase.*
- *Utilization of surrogate endpoints such as ICU admissions, non-invasive ventilation, and prolonged emergency room admissions.*

(Please see transcript for a detailed discussion)

Study Endpoints

2. A safety endpoint of asthma-related hospitalizations is proposed for the pediatric safety study. Discuss:

a) The adequacy of the primary endpoint to address the safety concerns of LABAs for the treatment of asthma in pediatrics
b) What level of risk for LABAs would be considered acceptable to rule out; i.e., what would be an acceptable upper bound of the 95% confidence interval?
c) Alternative endpoints that could be considered to evaluate the safety of LABAs for the treatment of asthma in pediatrics.

The committee members commented:

- *Hospitalization endpoint is adequate in this subset population.*
- *Agreed that a 95% confidence interval is sufficient and the absolute risk of 1% to 2% is acceptable to rule out.*
- *Recommended looking at tangible endpoints such as days of school missed, days of work missed by parents, nocturnal awakenings.*
- *It may be more appropriate to consider an observational case study to capture these events. They also stressed the need to obtain the evidence from an aggregation of data across multiple drug products.*

(Please see transcript for a detailed discussion)

Study Design

3. Given the hypothesis to be tested, discuss the advantages and disadvantages of a study design with a "real world" approach where patients enrolled are allowed titration of the inhaled corticosteroid (ICS) dose compared to a study design where the dose of ICS remains fixed. Which of these designs would be more appropriate to address the safety concerns of LABAs for the treatment of asthma?
Discuss:

a) in adults/adolescents

The committee members discussed that an observational study design would be better suited to characterize asthma deaths, frequency of access to care, and adherence to current asthma treatment guidelines, and allow calculation of baseline risk in the context of a cohort.

In addition, some members discussed that a controlled trial would not be able to capture the appropriate subset of patients at risk and pre-specified performance standards should be used with this method. Some members also commented on using a fixed ICS dose, but this approach conflicts with current reality. Additionally, further studies are needed to examine and determine appropriate step-down approaches in therapy. Others also commented on looking at smokers as another sub-group.

b) in pediatrics

The committee discussed the pros and cons of an observational study versus a randomized clinical trial. They had concerns of feasibility of enrollment and to ensure appropriate representation of the subset of high risk patients. Some committee members recommended that a fixed ICS dose should be used, but that it is not representative of the real world. Thus, others felt that allowing titration would be more realistic.

(Please see transcript for a detailed discussion)

Study Design

4. For a study design where the ICS dose remains fixed, discuss whether the ICS dose should be the same in the treatment arms or whether the ICS monotherapy group should have a higher dose. (Discuss)

Committee members commented on the following:

- *Use a fixed dose ICS in each group. Randomize those who need a step up from a low dose to a moderate dose ICS.*
- *Further looking at trial entry of stabilized patients versus patients who have not yet stabilized.*
- *Allow for a run-in period then randomization for symptomatic patients.*

(Please see transcript for a detailed discussion)

Length of Exposure

5. Discuss the adequacy of a 6 to 12 month treatment period to address the safety concerns of LABAs for the treatment of asthma
   a) in adults/adolescents
   b) in pediatrics
   c) Discuss the advantages and disadvantages of a shorter treatment period e.g. 3 months

The committee unanimously agreed on a 12 month trial for reasons dealing with seasonality, retention of subjects, and for better estimate assessments.

(Please see transcript for a detailed discussion)

6. Discuss what would be a reasonable timeframe for completion of the safety study.

The committee members agreed that five years is a reasonable timeframe.

(Please see transcript for a detailed discussion)

7. Given that data from the SMART study suggest a higher safety signal in African-Americans, and national statistics indicate a higher rate of serious asthma outcomes in the African-American population, a representative number of African-Americans are proposed for inclusion in the U.S. study sites. Discuss the challenges for obtaining meaningful information from sub-group analyses from the proposed study and possible options to address them.

Consider specific case control study to look at risk factors in the inner city population which can be done by reaching out to community groups, church groups, community health centers. In addition, a few members commented on looking at beta receptor polymorphisms in this sub-group.

(Please see transcript for a detailed discussion)

Ad hoc Question for the Committee:

After the committee deliberations on the Agency questions to the committee, the Chair posed to the committee whether a randomized clinical trial (RCT) can be undertaken based on the earlier discussions. Each committee member had the option to voice yes, no, or abstain.

Committee members opined on whether a large RCT should be undertaken and approximately two-thirds of the committee were in favor of a RCT. Those in favor of a RCT commented that a

large clinical trial with a composite endpoint with inclusions of hospitalization, non-invasive ventilation, and ICU admission to rule out a large absolute increase in risk is necessary. Others felt that a large clinical trial is not feasible and an observational study should be undertaken.

(Please see transcript for a detailed discussion)